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The first total synthesis of (±)-pallescensin B

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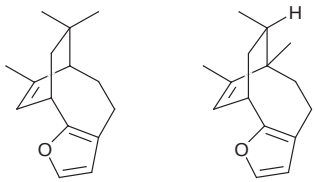
The first total synthesis of the title compound has been accomplished using an intramolecular Diels–Alder reaction of a masked *o*-benzoquinone, anionic [1,3]-rearrangement of a vinylbicyclo[2.2.2]octenol and intramolecular hetero-Michael addition of a hydroxy enone as the key steps.

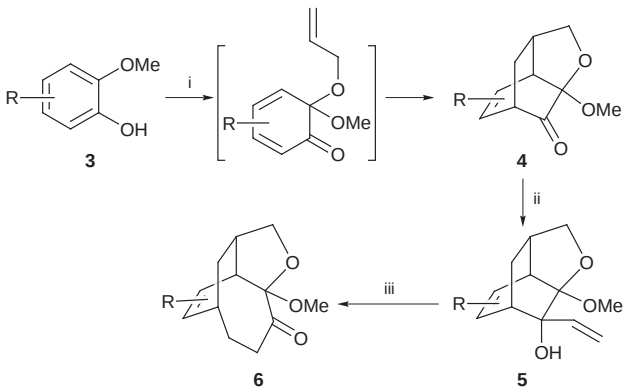
Pallescensins are a group of furanosesquiterpenoids isolated from the marine sponge *Disidea pallescens* by Cimino *et al*.[1] The common feature of these terpenoids is that they all contain a furan moiety; however they have carbon skeletons of varying complexity. Among the pallescensins, pallescensin B **1** presents the most complex architecture, with a unique bicyclo[4.2.2]decane system fused to a furan moiety. Interestingly, bicyclo[4.2.2]decane skeletons are relatively rare among natural products, the only other known example being nakafuran-8 **2**.[2]



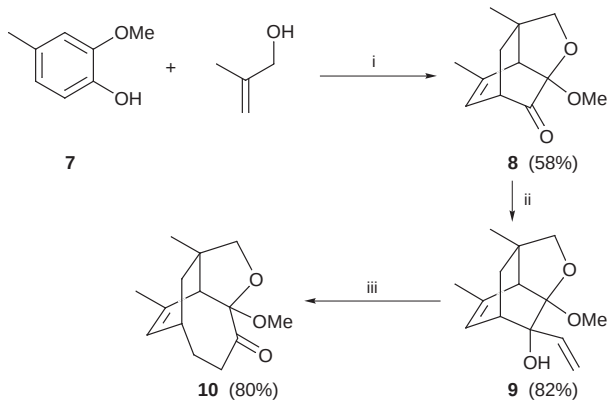
1 **2**

The synthesis of the bicyclo[4.2.2]decane skeleton poses a considerable challenge. Although a few methods exist for their synthesis,[2,3] they lack versatility and provide the desired skeleton only after several steps. Despite the long sequence of reactions it requires, Uyehara's approach to this skelecton is noteworthy.[2] Quite recently, we have developed a novel and efficient four-step methodology starting from 2-methoxyphenols, *via* anionic [1,3]-rearrangement of vinylbicyclo[2.2.2]-octenol derivatives as the key step, for the stereocontrolled synthesis of functionalized bicyclo[4.2.2]decenones (Scheme 1).[4] We herein report the first total synthesis of (±)-**1** clearly expressing the utility of the aforementioned methodology.

It was planned to use compound **10** as the key intermediate to achieve the synthesis of **1**, as we expected compound **9** to undergo anionic [1,3]-rearrangement. Synthesis of compound **10** was accomplished as shown in Scheme 2. Accordingly, the



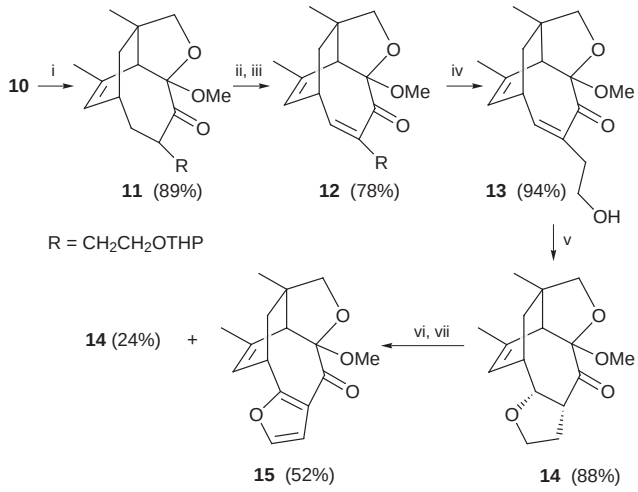
Scheme 1 *Reagents and conditions*: i, allyl alcohol, $PhI(OAc)_2$, CH_2Cl_2; ii, CH_2=CHMgBr; iii, KH, 18-crown-6.



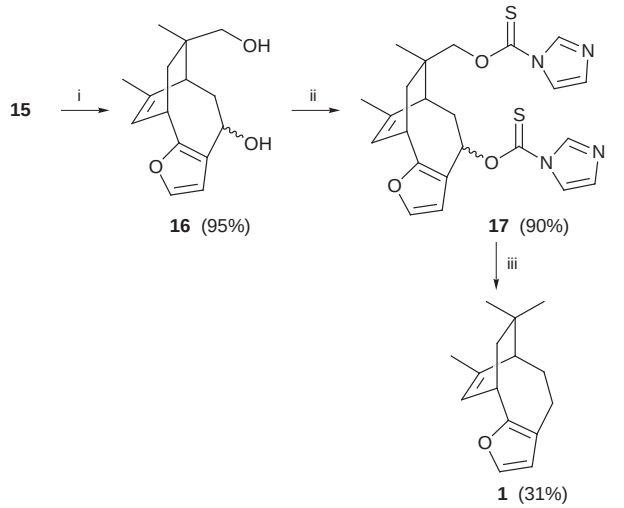
Scheme 2 *Reagents and conditions*: i, $PhI(OAc)_2$, $NaHCO_3$, 55–60 °C; ii, CH_2=CHMgBr, $ZnBr_2$, −78 °C to room temp.; iii, KH, 18-crown-6, 1,4-dioxane, reflux.

requisite bicyclo[2.2.2]octenone derivative **8** was prepared from 2-methoxy-4-methylphenol **7** in 58% yield, following a procedure developed in our laboratory for the synthesis of similar compounds.[5] Stereoselective addition of vinylmagnesium bromide to compound **8** in the presence of zinc bromide at −78 °C afforded **9** in 82% yield as the only discernible product. Subsequent anionic [1,3]-rearrangement of **9** proceeded smoothly to provide **10** in 80% yield (Scheme 2).

With compound **10** in hand, the stage is set for the construction of the furan ring, which was accomplished *via* seven synthetic steps, as shown in Scheme 3. The required two-carbon unit was introduced *via* alkylation of **10** using 1-bromo-2-(2-tetrahydropyranyloxy)ethane in the presence of KH at 0 °C in THF to obtain compound **11** in 89% yield as a 1:1 mixture of diastereomers. Then compound **11** was converted into the corresponding enone **12** using Saegusa's procedure[6] in two steps and in about 78% yield. The removal of the THP group was achieved *via* transacetalization with Pr^iOH catalyzed by PPTS to obtain the alcohol **13** as a single product. Intra-



Scheme 3 *Reagents and conditions*: i, RBr, KH, THF, 0 °C; ii, KH, TMSCl; iii, $Pd(OAc)_2$, MeCN; iv, Pr^iOH, PPTS, 55 °C; v, NaOH, MeOH, 80 °C; vi, KH, TMSCl; vii, DDQ, benzene, reflux.



Scheme 4 *Reagents and conditions*: i, SmI_2, MeOH, THF; ii, 1,1′-thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux; iii, Bu_3SnH, AIBN, toluene, reflux.

molecular Michael addition of **13** by treatment with 6 M aq. NaOH in MeOH at 80 °C furnished the tetrahydrofuran **14** as a single stereoisomer in 88% yield. The assigned stereochemistry of compound **14** was based on NOE experiments. Aromatization of **14** was accomplished *via* treatment of its silyl enol ether (KH, TMSCl) with DDQ in refluxing benzene to obtain the desired compound **15** in 52% yield, along with 24% of **14** (Scheme 3).

With construction of the complete carbon framework of **1** accomplished, the remaining task was to deoxygenate **15**. Towards this end, reduction of **15** with SmI_2 in the presence of MeOH was carried out first to obtain the diols **16** as a mixture of epimers,[7] which were converted then into a mixture of the corresponding bis-thiocarbamates **17** in 90% yield. The last hurdle to target compound **1** was passed by means of reduction of **17** with tin hydride initiated by AIBN in refluxing toluene (Scheme 4).[8] The structure of **1** was unambiguously established by its IR, ^1H and ^{13}C NMR, low and high resolution mass spectral data.[9] The UV, ^1H NMR and mass spectral data of synthetic (±)-**1** were found to be essentially identical with those reported by Cimino *et al*. for the natural product.[1]

Thus the synthesis of (±)-**1** was accomplished in 13 steps from readily available starting materials. In conclusion, the synthesis of (±)-**1** described here clearly exhibits the versatility of our methodology for the construction of the bicyclo[4.2.2]-decane skeleton and also confirms the structural assignments of the natural product.

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Notes and references

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9 *Selected data* for synthetic **1**: ν_{max}(neat)/cm^{-1} 2922 (s), 1505 (m), 1439 (m); δ_H(400MHz, $CDCl_3$) 7.07 (d, *J* 1.6, 1H), 6.03 (d, *J* 1.6, 1H), 5.81 (dq, *J* 6.9, 1.2, 1H), 3.43 (ddd, *J* 6.9, 6.6, 2.4, 1H), 2.36–2.28 (m, 1H), 2.21–2.04 (m, 3H), 1.92–1.84 (m, 1H), 1.60–1.53 (m, 2H), 1.79 (d, *J* 1.2, 3H), 0.91 (s, 3H), 0.77 (s, 3H); δ_C(100 MHz, $CDCl_3$) 153.2 (C), 141.2 (C), 138.0 (CH), 120.7 (CH), 118.1 (C), 113.5 (CH), 50.1 (CH), 43.8 (CH_2), 36.7 (CH_3), 33.8 (CH), 33.5 (C), 30.5 (CH_2), 29.9 (CH_3), 23.6 (CH_3), 22.0 (CH_2); *m/z* (70 eV) 216 (M^+); HRMS (EI): Calc. for $C_{15}H_{20}O$: 216.1514; found : 216.1504.

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